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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 06/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/793,653	DE SAUVAGE ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,16-26 and 28-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,16-26 and 28-30* is/are rejected.

7)☒ Claim(s) *26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 1997* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/12/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 3/14/05 has been entered in full. Claims 14, 16, 24, and 25 are amended. Claims 13 and 15 are canceled. New claims 29 and 30 are added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 14, 16-26 and 28-30 are under consideration in the instant application.

Submission of Missing References

The examiner thanks the Applicant for the submission of the references that were previously provided with an Information Disclosure Statement but that were not available at time of the previous Office Action. These references have been fully considered.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (9/13/04).

The rejection of claims 24-26 under 35 U.S.C. § 112, first paragraph at pg 2-4 for failing to provide enablement for methods of treatment of type I diabetes or bulimia is withdrawn. Please see the new rejection of claims 24-26 under 35 U.S.C. § 112, first paragraph below. Applicant's argument regarding the previous rejection as they pertain to the new rejection are addressed after the new rejection.

The rejections of claims 13 and 15 under 35 U.S.C. § 102(e) and 103 at pg 5-9 are withdrawn in view of the cancelled claims (3 March 2005). Please see the new claim rejections under 35 U.S.C. § 102(e) and 103 below.

Please see new claim objections and rejections, below.

Claim Objections

Claim 26 depends from claim 13, which is currently cancelled. Appropriate correction is required. The examiner notes that the limitations of claim 13 have been incorporated into claim 14. Therefore, for purposes of prosecution, claim 26 will be interpreted as if it depended from claim 14.

Claim Rejections - 35 USC § 112, 1st paragraph, scope of enablement

Claims 24-26 and 29-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) a method of treating a condition associated with a homozygous mutation in the OB (leptin) gene, or a method for eliciting a biological response in rodents, or humans with said homozygous mutation, wherein the biological response is a decrease in food intake or an increase in energy use comprising administering the claimed chimeric polypeptide, and 2) compositions for the treatment of obesity associated with a homozygous mutation in the OB gene, does not reasonably provide enablement for 1) a method of treating a condition associated with the abnormal expression or function of the OB gene or for eliciting a biological response mediated by an OB receptor, or 2) a composition for the treatment of obesity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The specification teaches that an OB-immunoglobulin (OB-Ig) fusion is more effective than native OB at reducing body weight and food intake in obese *ob/ob* female. The term *ob/ob* indicates the mice are homozygous for a mutation in OB gene.

Claim 24 encompasses a method comprising administering to a patient a therapeutically effective amount of a chimeric OB-Ig fusion protein. The method is intended for treating any condition associated with the abnormal expression or function of the OB gene, or for eliciting any biological response mediated by an OB receptor. The specification contemplates that obesity, bulimia, type I diabetes and type II diabetes belong to the genus of conditions associated with abnormal expression of or function of the OB gene. Claim 25 depends from claim 24 and limits said conditions to obesity, bulimia, and type I or type II diabetes. The nature of the invention of Claim 26 is a composition for the treatment of obesity comprising an effective amount of a chimeric polypeptide of claim 14 [see Claim Objections above] in association with a pharmaceutically acceptable carrier. Claims 29 and 30 depend from claim 24 and limit the biological response mediated by an OB receptor to a decrease in food intake or an increase in energy use.

The relevant art teaches that, other than individuals with homozygous mutations in the OB gene, it is not possible to identify obese individuals for which OB treatment is effective in treating obesity. Gale teaches that "rare genetic mutations resulting in leptin or leptin receptor deficiencies in humans also support the notion that leptin plays an important role in satiety...administration of exogenous leptin to these [leptin-deficient] children results in a remarkable decrease in their energy intake and a dramatic loss of fat mass while maintaining lean body mass. Although these studies demonstrate that leptin can be a most effective pharmaceutical preparation for treating obesity in leptin-deficient states, the administration of exogenous leptin fails to reduce adiposity significantly in most cases of human obesity that are characterized by increase adipocyte leptin content and high circulating leptin levels, reflecting a state of leptin resistance" (Gale et al, 2004, Recent Advance in Nutritional Sciences. J Nutr. 2004 Feb;134(2):295-8). Bell-Anderson teaches that in the first human trials where leptin was administered, "there was considerable variability in the amount of weight lost. There were also large variations in reported reductions in energy intake, although those patients who received the largest dose of leptin reported lower energy intake. It appears that in some hyperleptinemic patients, leptin may be useful as a treatment option. The

problem is identifying which patients would benefit from this form of therapy" (Bell-Anderson et al, 2004. Treat Endocrinol. 3(1):11-18).

Therefore with respect to obesity and type II diabetes, while the relevant art supports that obesity (and type II diabetes as it is generally linked with obesity) is characterized by abnormal expression of leptin (encoded by the leptin gene), the relevant art teaches that administration of leptin only predictably treats those patient with abnormally low expression of leptin due to a homozygous mutation in the leptin gene.

With respect to bulimia and type I diabetes, the relevant art does not support that these diseases are associated with abnormal expression of the OB gene. The prior art teaches that type I diabetes "is not associated with obesity" (Ganong, 1989. Review of Medical Physiology, pages 299-300; cited in the previous Office Action). Furthermore, the relevant art does not teach that type I diabetes is associated with low levels of leptin or that administration of leptin would treat type I diabetes. Similarly, the relevant art teaches in a bulimic patient, "although binging and purging episodes were quite frequent, leptin levels remained stable and were neither related to food intake nor to binge episodes" (Abstract of Herpetz et al, May 1998 May; 23(4): 459-653; cited in the previous Office Action), and "although bulimic patients have very bad nutritional behavior, their leptin levels do not appear altered" (Abstract of Calandra, et al, June 2003; 8(2): 130-7; cited in the previous Office Action). To date, the art has not established a connection abnormal expression of the OB gene and type I diabetes, or bulimia.

Therefore, while the specification asserts that the OB-Ig protein of the invention can be used to treat any disorder or condition associated with abnormal OB gene expression, the relevant art teaches that only individuals with a homozygous mutation in the OB gene can be treated with leptin. Furthermore, the relevant art does not teach that the levels of leptin in patients with bulimia or type I diabetes are abnormally low, so that one of skill in the art would predict that said conditions could be treated with leptin.

The specification does not provide any guidance as to what other conditions are associated with the abnormal expression or function of the OB gene, or what biological conditions are associated with an OB receptor other than food intake and energy use.

The quantity of experimentation needed to make and use the invention as claimed would be undue because in order to use the full scope of the claimed invention, a person of skill in the art would need to engage in further experimentation to:

1) identify those obese or type I patients (other than those with homozygous mutations) that can be treated with the OB-Ig of the invention.

2) identify patients with type I diabetes or bulimia that have abnormal expression or function of the OB gene, and then test whether administration of an OB-Ig fusion protein would or would not treat the condition of type I diabetes, or bulimia.

3) identify individuals in which a biological response of a decrease in food intake or an increase in energy use occurs when administered the OB-Ig fusion.

It is acknowledged that the level of skill of those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification how the OB-Ig of the present invention could be used to treat a patient with a condition associated with the abnormal expression or function of the OB gene or to elicit a biological response associated with the OB receptor, or how a composition comprising OB-Ig and a pharmaceutically acceptable carrier could be used to treat obesity. There are no methods or working examples disclosing treatment of conditions associated with abnormal expression or function of the OB gene, or disclosing elicitation of a biological response mediate by an OB receptor, with the claimed OB-Ig. Thus the specification fails to teach the skilled artisan how to use the method or composition for treatment or elicitation without resorting to undue experimentation. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use the method or composition for the above stated purpose.

Due to the large quantity of experimentation necessary to determine if the method or composition could be used for treatment of conditions associated with abnormal expression or function of the OB gene or for elicitation of a biological response mediate by an OB receptor, the lack of direction/guidance presented in the

specification regarding same, lack of working examples and the teachings of the relevant art regarding the unpredictability in identifying obese patients that respond to OB treatment and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention. What Applicant has provided is a mere wish or plan and an invitation to experiment.

In the response dated 3/14/05 Applicant submits that the method of claims 24 and 25 are enabled for treatment of type I diabetes or bulimia because the specification establishes that there is a nexus between the disorders and the OB protein, and the quantity of experimentation to use the invention would not be undue because this nexus has been established. Applicant further submits that other factors support that the claims are enabled including, the high skill in the art of the practitioners in molecular biology arts at the time the invention was made, the claims are directed to a finite number of identifiable disorders and are therefore not excessively broad, and the methods use a compound that was and is fully enabled, and therefore the method using should also be fully enabled.

Applicant's arguments have been fully considered but are not found persuasive for the following reasons. While the specification states that there is a connection between type I diabetes or bulimia and the OB protein, this asserted connection is not sufficient to enable one of skill in the art to practice the claimed method with these conditions. The examiner agrees the skill in the art was high at the time the invention was made, but it would still require undue experimentation, for the reasons outlined in the new enablement rejection detailed above, to practice the claimed method to treat these conditions. While the claims are limited to a finite number of identifiable disorders, the specification does not enable one of skill in the art to treat even those identifiable disorders. The fact that a product is enabled does not enable each and every possible method of use of the product is also enabled, and the instant method of use is not enabled for the reasons detailed above.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 recites the limitation "the chimeric polypeptide" in lines 3-4 . There is insufficient antecedent basis for this limitation in the claim. In this regard, claim 24 would be rendered definite if this limitation was amended to read "a chimeric polypeptide".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 24, 25, 29 and 30 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Pellymounter et al, U.S. Patent Application Publication No. 2003/0203837, filed 5/30/2003 and meriting priority to 11/22/1995 (cited in the previous Office Action).

Claims 24 and 25 each encompass a method comprising administering to a patient a therapeutically effective amount of a chimeric protein comprising a native OB protein with an initiating N-terminal methionine fused to an immunoglobulin heavy chain constant domain sequence. The recitation of "treating a condition associated with the abnormal expression or function of the OB gene or for eliciting a biological response mediated by the OB receptor" in the preamble of the claim is interpreted as an intended

use and bears no accorded patentable weight, except in so far as it limits the "patient" to those with "a condition associated with the abnormal expression or function of the OB gene". Dependent claim 25 limits these conditions to obesity, bulimia, and type I or II diabetes. The specification does not define or limit a "therapeutically effective amount" and therefore the term encompasses any amount that is effective for any therapy.

Pellymounter teaches (page 8, Example 5) administration of a OB protein derivative to a diabetic patient. Pellymounter teaches (paragraph 31) that derivatives of the OB protein include fusion proteins that "may be prepared by attaching polyaminoacids to the OB protein (or analog) moiety. For example, the polyamino acid may be a carrier protein which serves to increase the circulation half-life of the protein. Such polyamino acid may be selected from the group consisting of ...an antibody or portion thereof (such as an antibody constant region, sometimes called "Fc").... As indicated below, the location of attachment of the polyamino acid may be at the N-terminus of the OB protein moiety, or other place, and also may be connected by a chemical "linker" moiety to the OB protein." The term Fc refers to a part of the antibody consisting of only heavy chain constant domain sequences. Pellymounter teaches (paragraph 16, lines 3-4) that the OB protein used may be the human OB protein according to Zhang et al (Reference 37 of the IDS filed 12-3-1998). The sequence taught by Zhang in Figure 6b (page 430) is the "sequence of human OB protein" and includes an initiating N-terminal methionine and a native signal sequence. Pellymounter, in claim 1, teaches "A fusion protein optionally having an N-terminal methionine comprising an antibody constant region or portion thereof attached to the N-terminus of an OB protein." Pellymounter (paragraph 66, lines 1-3) further teaches "One skilled in the art will be able to ascertain effective dosages by administration and observing the desired therapeutic effect." Therefore, Pellymounter teaches a method comprising administering to an diabetic patient a therapeutically effective amount of a chimeric polypeptide that clearly anticipates instant claims 24 and 25.

Claims 29 and 30 encompass a method of increasing energy use or decreasing food intake by administering to a patient a polypeptide of claim 24. The limitations recited in claims 29 and 30 modify the preamble of claim 24 and are therefore

interpreted as an intended use and bear no accorded patentable weight, except in so far as they limit the "patient" to which the chimeric polypeptide will be administered. However, neither the claim nor the specification defines a patient population for which food intake or energy use should be administered; therefore the claim encompasses any type of patient (e.g., obese, diabetic, or healthy). The claim encompasses a method comprising administering to an obese patient a chimeric polypeptide with the limitations of claim 24, and as described above Pellymounter teaches a method with these limitations, and therefore clearly anticipates claims 29 and 30.

Claim Rejections - 35 USC § 103

Claims 14, 16-23, 26, and 28 are rejected under 35 U.S.C. 103 as being unpatentable over Pellymounter et al, U.S. Patent Application Publication No. 2003/0203837, filed 5/30/2003 and meriting priority to 11/22/1995, in view of Capon et al, U.S. Patent No. 5,455,165, published 10/3/1995.

As described above, Pellymounter teaches a chimeric polypeptide comprising the amino acid sequence of a native OB protein, with the N-terminal methionine and with the native signal sequence, fused to Fc region of an antibody, which is an immunoglobulin heavy chain constant domain sequence that comprises the hinge, CH2, and CH3 regions. Pellymounter further teaches (page 2, paragraph 16) a nucleic acid sequence encoding a native human OB protein.

Pellymounter does not teach, that the immunoglobulin constant domain sequence comprises the hinge, CH2, and CH3 regions of an IgG (as in claim 14); or that two chimeric OB polypeptide IgG heavy chain fusion as are linked to each other by at least one disulfide bond (as in claim 16); or the chimeric polypeptide of claim 16 wherein at least one of the heavy chain fusions is associated with an immunoglobulin light chain (as in claim 17); or an isolated nucleic acid molecule encoding the chimeric polypeptide comprising a chimeric polypeptide comprising the amino acid sequence of a native OB protein, with the N-terminal methionine and with the native signal sequence, fused to an immunoglobulin heavy chain constain domain sequence (as in claim 18); or a replicable expression vector comprising said nucleic acid (as in claim 19); or a host

cell transformed with said vector (as in claim 20); or a process of culturing said host cells so that said nucleic acid is expressed and said chimeric polypeptide is produced, and recovering said polypeptide (as in claim 21); said process wherein said host cells are cotransformed with nucleic acid encoding at least two OB protein-immunoglobulin heavy chain constant domain fusions (as in claim 22); or said process wherein said cells are further transformed with nucleic acid encoding at least one immunoglobulin light chain (as in claim 23); or a composition comprising an effective amount of a chimeric polypeptide of claim 14 with a carrier (as in claim 26); or a nucleic acid encoding a chimeric polypeptide comprising a mature native human OB polypeptide fused at its C-terminus, to the N-terminus of an IgG constant domain sequence comprising the hinge, CH2 and CH3 regions (as in claim 28).

Capon teaches general techniques for "compositions and methods for improving the circulating half-life of ligand binding molecules...hybrid immunoglobulin molecules, to methods for making and using these immunoglobulins, and to nucleic acids encoding them." Capon further teaches (col 9, lines 56-58) that "typically, such fusions retain at least functionally active hinge, CH2, and CH3 domains of the constant region of an immunoglobulin heavy chain." Capon further teaches (col 13, 53-55) that "immunoglobulin combining sites and fusion partners are obtained from ... preferably IgG-1." Capon teaches general techniques for "compositions and methods for improving the circulating half-life of ligand binding molecules...hybrid immunoglobulin molecules, to methods for making and using these immunoglobulins, and to nucleic acids encoding them." Capon further teaches (col 9, lines 56-58) that "typically, such fusions retain at least functionally active hinge, CH2, and CH3 domains of the constant region of an immunoglobulin heavy chain." Capon further teaches (col 10, lines 35-65 and col 11, lines 2-3) homodimers consisting of protein-constant domain fusions that are "disulfide bonded in the same fashion as native immunoglobulins". Capon further teaches (same section) that the homodimers can be associated with immunoglobulin light chains; Capon further teaches (col 14, lines 26-38) nucleic acids encoding a protein fused to an immunoglobulin heavy chain constant domain region; Capon further teaches (col 25, lines 7-9) expression hosts transformed with DNA encoding the hybrid which has been

ligated into an expression vector. Capon further teaches (col 28, lines 1-2) that "host cells are transformed with expression vectors of this invention and cultured in conventional nutrient media..." and (col 28, lines 1-2) "the novel polypeptide is recovered and purified from recombinant cell cultures..." Capon further teaches (col 15, line 6-9) "multiply cotransformed cells are used with the above-described recombinant methods to produce polypeptides having multiple specificities..." Capon further teaches (col 14, 61-63) "If multimers are desired then the host cell is transformed with DNA encoding each chain that will make up the multimer"; Capon further teaches (col 5, lines 66-67) formulations of the hybrid immunoglobulins of the invention with pharmacologically acceptable vehicles; and Capon further teaches (col 9, lines 48-49) that "Ordinarily, the ligand binding partner is fused C-terminally to the N-terminus of the constant region of the immunoglobulins..."

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the OB-Fc fusion taught by Pellymounter to use any of the above teachings of Capon. The person of ordinary skill in the art would be motivated to do so because Pellymounter teaches Fc fusions and Capon teaches generic modifications of a hybrid immunoglobulin that can be used to prolong the in vivo plasma half-life of a protein to which the immunoglobulin is fused, and each of the above modifications is taught by Capon as examples of ones that will prolong the half-life of the protein. One of skill in the art would expect success because Pellymounter teaches OB-Fc fusions and Capon teaches all of the techniques necessary to make the modified OB-Fc fusions described above.

Claims 14,16-26, 28, 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Zhang et al, Basinski et al ('744 or '886), DiMarchi et al ('954 or '336), in view of Shin et al, or Ashkenazi et al. The basis for this rejection is set forth for claims 14, 16-26 and 28 at pg 7-8 of the previous Office Action of 5/27/1998, and for claim 28 at pg 9 of the previous Office Action 9/13/2004.

Applicant's arguments (3/14/05), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicants submit that this rejection (set forth 5/27/1998) was withdrawn (3/12/1999) by a previous Examiner in response to the amendments and arguments by Applicants. Applicants note that the USPTO has a duty to apply consistent standards in examining patent applications. Applicants suggest that, as there was no statement that the decision was reversed, the instant Examiner may have overlooked the withdrawal of the rejection made by the previous Examiner. Applicants submit that this position is supported by the statement in the previous Office Action that that the rejection is "is maintained" when in fact the rejection was previously withdrawn. Applicants note MPEP § 706.04 and submit that the previous argument were sufficient to overcome the rejections.

Applicant's arguments have been fully considered but are not found persuasive. The Examiner fully considered the 3/12/1999 withdrawal of the rejection of 5/27/1998 by the previous Examiner. The Examiner of this application has changed and although the USPTO has a duty to apply consistent standards the current Examiner is not bound to repeat mistakes made by the previous Examiner. The Examiner does concede that the statement "is maintained" was not correct in that the rejection had been withdrawn by the previous Examiner. Therefore, the Examiner indicates now for the record the withdrawal of 3/12/1991 is reversed, and the rejection of 5/27/1998 is re-entered.

Applicants also note that the references cited by the Examiner are not as relevant as the references cited by the Applicants in their previous Response. Applicants assert that the references in the previous Office Action (e.g., Shin et al and Ashkenazi et al) are not directed to the relevant protein (OB protein), while the references (Maffei et al, Coleman and Campfield et al) are directed to the relevant protein (OB protein). Applicants submit that the entirety of the prior art must be considered and that one of skill in the art would not have ignored references directly relevant to the protein and questions at hand, and instead look to teachings in unrelated proteins or systems. Applicants disagree with the Examiner's position that the fact that "earlier OB protein studies may not have fully recognized the nature of the interaction

with its cognate receptor, and where such receptors are located, does not detract from the obviousness" (page 7). Applicants argue that to the contrary what one of skill in the art at the time of invention would have believed or not believed concerning OB protein studies and the location of the receptor directly impacts what one of skill in the art would have been motivated to do and would have expected as an outcome. Applicants submit that it was a fact that those of skill in the art believed that these proteins were expressed in the brain and that this fact would suggest that anything that targets the protein would need to be able to pass the blood brain barrier.

Applicant's arguments have been fully considered but are not found persuasive. The examiner agrees that the references Shin et al and Ashkenazi et al are not directed to the relevant reference. However, they were included in the rejection as secondary references used in an obviousness type rejection, and they provide teachings towards making immunoglobulin-protein fusions that are generally applicable to any protein. The primary references used, Zhang et al, Basinski et al ('744 or '886), DiMarchi et al ('954 or '336), discuss the relevant OB protein. The examiner agrees that one of skill in the art would not have ignored the relevant teachings of Maffei et al, Coleman and Campfield et al. However, the teachings of Maffei et al, Coleman and Campfield et al. do not detract from the obviousness of Zhang et al, Basinski et al ('744 or '886), DiMarchi et al ('954 or '336), in view of Shin et al, or Ashkenazi et al. The examiner disagrees with the statement that it was a fact "that that those of skill in the art believed that these proteins were expressed in the brain." Maffei (cited by Applicants) teaches (page 6959) "Mechanisms involving the circumventricular organ and/or specific transporters could permit brain access of a molecule the size of that encoded by the OB gene. However, this hypothesis must considered with caution until the means by which the protein might cross the blood-brain barrier have been identified. Moreover, possible effects on other target organs will need evaluation." Therefore, Maffei teaches clearly states that a brain location of the OB receptor was just a hypothesis and indicates there are alternate hypotheses that it acts on other organs. Furthermore, Maffei suggests a hypothetical scenario by which a molecule the size of OB might enter the brain. There is nothing in this proposed hypothesis that teaches away from a larger OB-Ig fusion entering the

brain by the same mechanism. As cited in the previous Office Action at pg 8, it was known in the art at time the invention was made that transfferin-Ig fusions could penetrate the blood-brain barrier more effectively than transferrin alone. Therefore, Maffei clearly suggests 1) there are possibly ways for large molecules such as OB to enter the brain and 2) OB may work at receptors at other locations besides the brain. Therefore, the Examiner maintains that the prior art, while not fully recognizing the nature of the interaction between OB and its receptor, and where the receptor is located, does not detract from the obviousness of constructing a OB leptin fusion.

New claims 29 and 30 encompass a method of increasing energy use or decreasing food intake by administering to a patient a polypeptide with the same limitations as claim 24. The limitations recited in claims 29 and 30 modify the preamble of claim 24 and are therefore interpreted as an intended use and bear no accorded patentable weight, except in so far as they limit the "patient" to which the chimeric polypeptide will be administered. However, neither the claim nor the specification defines a patient population for which food intake or energy use should be administered; therefore claim encompasses any type of patient (e.g., obese, diabetic, or healthy). Therefore, the claim encompasses a method of comprising administering to an obese patient a chimeric polypeptide with the limitations of claim 24, and are unpatentable in view of the above cited references for the same reasons of record as for claim 24.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

zch

Bridget E. Bunner
patent examiner